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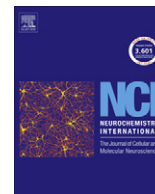
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Motor behavior correlates with striatal [^{18}F]-DOPA uptake in MPTP-lesioned primates

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ABSTRACT

The MPTP-lesioned monkey is considered as the best animal model for Parkinson's disease (PD). It has damage to dopaminergic cell groups and motor dysfunction similar to that seen in PD. Correlations between these two parameters have been described but there is a lack of formal statistical analyses on dopaminergic function as assessed by [^{18}F]-F-DOPA PET and objectively rated motor behavior in longitudinal experiments.

Eight rhesus monkeys received two MPTP infusions: first in one carotid artery, and after eight weeks in the other. Motor behavior and [^{18}F]-F-DOPA uptake were measured at three stages: baseline, unilateral and bilateral. We correlated movement with radiotracer uptake across these three stages. MPTP caused the expected parkinsonian motor signs which were accompanied by lower radioactivity concentrations in the striatum. There were significant correlations between dopaminergic function and behavior.

In conclusion, striatal [^{18}F]-F-DOPA uptake correlates inversely with the severity of motor impairment in MPTP-lesioned non-human primates. Both behavioral scoring and [^{18}F]-F-DOPA PET scans are useful and sensitive methods to monitor dopaminergic degeneration within subjects.

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1. Introduction

Parkinson's disease (PD) affects about one in a hundred people above 65 years of age. It is best known as a movement disorder, associated with tremor, rigidity and bradykinesia but it is also associated with a high incidence of depression, subtle cognitive deficits and a reduced life expectancy. The most conspicuous brain change in PD is the degeneration of dopaminergic neurons in the substantia nigra pars compacta as found in *post mortem* studies. The cause of PD is unknown and there is currently no cure.

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a synthetic neurotoxin that induces parkinsonism in humans (Langston et al., 1983) and also in monkeys (Kolata, 1983). It destroys monoaminergic neurons with dopaminergic neurons being especially sensitive. As a result MPTP induces among others depletion of dopamine in the striatum. Because of the neurochemical and behavioral parallels, the MPTP-lesioned non-human primate is considered as the best model for PD (Saiki et al., 2010) and it is

used to study the pathophysiology of PD and to evaluate candidate treatments for PD.

For the evaluation of potential neuroprotectants in PD models and for clinical studies alike it is important to study both motor behavior and neurochemistry. Motor behavior can be quantified objectively for the characterisation of the severity of movement disorders and parkinsonian symptoms in non-human primates (Kurlan et al., 1991).

Neuroimaging of the dopaminergic system is possible with positron emission tomography (PET) or single photon emission computed tomography (SPECT) in combination with a dopaminergic tracer. SPECT can image the dopamine transporter with [^{123}I]-β-CIT ([^{123}I]-2-β-carbomethoxy-3-β-(4-iodophenyl)-tropane) and PET can measure the dopamine synthesis capacity of the nigrostriatal system with [^{18}F]-F-DOPA (6-[^{18}F]-fluoro-L-3,4-dihydroxy-phenylalanine) or [^{18}F]-FMT (6-[^{18}F]-fluoro-L-m-tyrosine).

There is a good correlation between *post mortem* and neuroimaging findings in humans (Snow et al., 1993). There is also a good correlation between neuroimaging findings and clinical severity in PD patients (Garnett et al., 1984).

For the validity of the MPTP lesioned primate as a model for PD it is important to establish that it also displays strong correlations between motor behavior and nigrostriatal dopaminergic function as indexed by neuroimaging. Indeed this has been established for

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a large part. Motor symptoms in MPTP-lesioned monkeys correlate with the uptake of [^{123}I]- β -CIT (Eberling et al., 1999) and [^{18}F]-FMT (Hayase et al., 1995) in that low uptake coincides with bradykinesia and rigidity. A correlation also exists between motor behavior and the dopamine transporter tracer [^{11}C]-CFT uptake in a two group design (Saiki et al., 2010). Also for [^{18}F]-F-DOPA, across four groups of differentially affected MPTP lesioned monkeys, significant correlations exist between striatal [^{18}F]-F-DOPA uptake and motor behavior (Blesa et al., 2010). One of the few longitudinal studies (de Yebenes et al., 1998) showed that there is an association between motor behavior and [^{18}F]-F-DOPA uptake but they did not do a formal correlation analysis on their data.

What is not well established is the correlation between motor behavior and [^{18}F]-F-DOPA uptake within the same MPTP lesioned monkeys, while this is typically a situation that resembles the clinical situation: repeated [^{18}F]-F-DOPA scans are used to document disease progress within individual PD patients. We aimed to study the correlation between motor symptoms and striatal uptake of [^{18}F]-F-DOPA PET in MPTP-lesioned monkeys in a quantitative manner and hypothesized that a strong correlation would exist. We had access to data from a longitudinal experiment in eight monkeys in which all monkeys were scanned three times with PET.

2. Materials and methods

2.1. Subjects

A total of eight right-handed young adult male rhesus monkeys were studied under an approved protocol that met all institutional guidelines and requirements stated in the 'Principles of Laboratory Care' (NIH publication No. 85–23, revised 1985). All efforts were made to minimise animal suffering, to reduce the number of animals used, and to utilize alternatives to *in vivo* techniques, if available.

No extra monkeys were used for the current research because they participated in a drug trial investigating a candidate neuroprotective substance: TCH346 aka CGP3466(B) (see also (Andringa et al., 2003)). The substance has antiapoptotic effects and a very favourable profile in animal models of neurodegenerative diseases such as PD and multiple sclerosis (MS) (Mück-Seler and Pivac, 2000; Andringa G., 2000; Andringa et al., 2003). Unfortunately, it failed as a neuroprotectant in both PD (Olanow et al., 2006) and MS patients (Miller et al., 2007).

The monkeys weighed between six and twelve kilograms and were individually housed in cages under standard conditions. Diet consisted of lab chow supplemented with fruit while water was available *ad libitum*.

2.2. MPTP treatment

A two-phase bilateral MPTP lesion approach was used to generate bilateral parkinsonism. This treatment induces moderate to severe parkinsonian symptoms with a significant reduction in limb movements and decreased striatal [^{18}F]-F-DOPA uptake (Smith et al., 1993).

Under total anesthesia a first dose of 2.5 mg MPTP was administered into the carotid artery contralateral to the dominant limb (unilateral stage) and, eight weeks later, a second dose of 1.25 mg MPTP was infused into the other carotid artery (bilateral stage). The second dose was lower to limit incapacitation of the animals.

Four out of the eight monkeys received TCH346 at several dose levels for the next fourteen days after the second injection. The other four monkeys received saline. It was assumed that while this compound may have retarded neurodegeneration in this model, it

does not alter the relationship between dopaminergic function and behavior.

2.3. Assessment of motor symptoms

Motor symptoms were assessed with validated quantitative behavioral observation. Monkeys were observed and videotaped for 1 h on each test day: at 10 and 3 days prior to the first MPTP treatment (naïve stage), at 6 and 7 weeks after the first MPTP treatment (unilateral stage) and at 3, 7, 14, 21, 28 and 35 days after the second MPTP treatment (bilateral stage). A single trained investigator, blind to the treatments, evaluated motor symptoms using two different rating scales.

The first scale was a qualitative assessment of *parkinsonian symptoms* using a rating scale for non-human primates (Kurlan et al., 1991), with minor modifications for bilaterally treated MPTP monkeys (Smith et al., 1993). This clinically oriented rating scale included the items: tremor, gait, akinesia/bradykinesia, balance, rigidity/posture and food intake. The total *parkinsonian symptoms* score was obtained as the sum of all items.

The second rating scale was a quantitative assessment of *goal-directed limb movements* per body half (Andringa et al., 1999) and is expressed as the percentage of time spent on goal directed limb movements. Decreased values indicate increased parkinsonian signs.

Given the lack of significant differences between the values at the several time points in each stage, these were averaged per stage.

2.4. Scanning procedures

All monkeys were scanned at baseline (1 week prior to the first MPTP lesion), in the unilaterally lesioned state (7 weeks after the first lesion) and in the bilaterally lesioned state (ca. 5 weeks after the second lesion).

Handling, transportation, sedation, scanning, monitoring of vital signs, administration of drugs and radiotracer have been described before (Kortekeas et al., 2008) but for this experiment the anesthetic carrier gas was $\text{O}_2:\text{N}_2\text{O}$ (50:50) instead of pure oxygen. Another modification of the previous protocol was that the peripheral decarboxylase inhibitor carbidopa was administered orally (3 mg/kg) 30 min before [^{18}F]-F-DOPA administration. The heads were supported in a stereotactic frame and positioned centrally in the field of view of the scanner. An average of 98.2 MBq (range: 22–167) of [^{18}F]-F-DOPA in 6 mL of physiological saline was injected IV over one minute. Scanning was initiated immediately and 21 frames were acquired (10×30 , 3×300 , 4×600 , 4×900 s, totaling 120 min). One monkey's PET scan failed in the unilateral phase due to a technical problem. Data from the unilateral stage were not used for the correlation analyses.

2.5. PET data analysis

PET data were reconstructed to a $128 \times 128 \times 63$ matrix with a plane separation of 0.2425 cm and a bin size of 0.2250 cm. Using the Clinical Applications Programming Package (Siemens, Erlangen, Germany), regions of interest (ROIs) were placed by hand on PET data collected from 60–120 min: elliptical ROIs were placed on three planes over the left and right striatum, and as a reference, on the posterior half of the brain (see Fig. 2). The reference region included cortical grey and white matter and was of a deliberately large size to minimize intersubject variability in placement. The rate of specific uptake into the striatum (K_{ref} values) relating tracer uptake to the reference brain region, was calculated (Dhawan et al., 2002). Mean striatal uptake was calculated as the average of left and right striatal uptake.

2.6. Statistics

For the statistical analysis, the three measurements in the eight subjects were treated as independent because there had always been a new lesion between any two measurements, thereby violating the assumption of dependence within subjects. Because one PET measurement was missing, this resulted in a total of 23 observations. Because data were not normally distributed according to the Shapiro Wilk test, we calculated Spearman's rho, two-tailed. A p value <0.05 was considered significant.

3. Results

3.1. [^{18}F]-F-DOPA uptake

Before injection of MPTP, mean [^{18}F]-F-DOPA uptake for left and right striatum was 0.00208 ± 0.00025 ($K_{\text{ref}} \pm \text{S.D.}$, see Table 1). An example of a transaxial slice through the striatum is shown in Fig. 2.

Unilateral administration of MPTP resulted in a significant decrease of left [^{18}F]-F-DOPA striatal uptake, see Table 1 ($p = 0.01$; paired t -test, two-tailed). In contrast, [^{18}F]-F-DOPA uptake in the right striatum was increased, but not significantly ($p = 0.16$; paired t -test, two-tailed).

After administration of MPTP into the right carotid artery, [^{18}F]-F-DOPA uptake in the right striatum was decreased in the four monkeys receiving saline, although not as much as after the first application of MPTP. [^{18}F]-F-DOPA uptake in the right striatum stayed within the normal range in the TCH346 treated group. There was no effect of the second application of MPTP on [^{18}F]-F-DOPA uptake in the left striatum.

3.2. Motor scores

Before injection of MPTP, all monkeys displayed normal motor behavior (Fig. 1 and Table 2). No signs of parkinsonism were

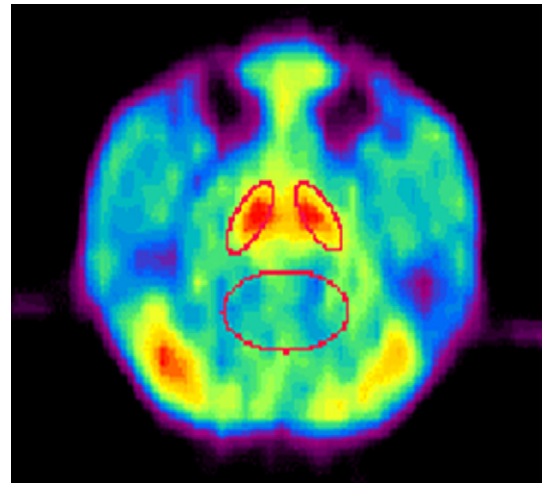


Fig. 2. Position of the regions of interest (red ovals) on a [^{18}F]-F-DOPA PET scan in the baseline state. A transaxial slice at the level of the striatum is given with the nose up. Small ovals contain the striatum, the large oval is a control region, containing supracerebellar occipital cortex, that receives no measurable dopaminergic input. Image was made with CAPP5 (Siemens, Erlangen, Germany). (For interpretation of color in this figure the reader is referred to the web version of this article.)

Table 2

Parkinsonian symptoms (mean \pm standard deviation) in the three stages of the experiment.

Stage	Limb movements left	Limb movements right	Total parkinsonian symptoms
Baseline	10.28 ± 5.70	18.18 ± 9.70	0.0 ± 0.0
Left lesion	10.11 ± 4.70	3.94 ± 3.40	1.69 ± 1.90
Bilateral lesion	6.26 ± 6.00	3.76 ± 2.50	9.87 ± 5.90

Table 1

Striatal uptake (K_{ref}) of [^{18}F]-F-DOPA (mean of all monkeys \pm standard deviation) for the three experimental stages. Mean uptake is the average of left and right. Data are presented as group mean \pm standard deviation.

Stage	K_{ref} left	K_{ref} right	K_{ref} mean
Baseline	0.00211 ± 0.00039	0.00204 ± 0.00025	0.00208 ± 0.00025
Left lesion	0.00055 ± 0.00097	0.00271 ± 0.00098	N/A
Bilateral lesion	0.00035 ± 0.00041	0.00175 ± 0.00130	0.00118 ± 0.00066

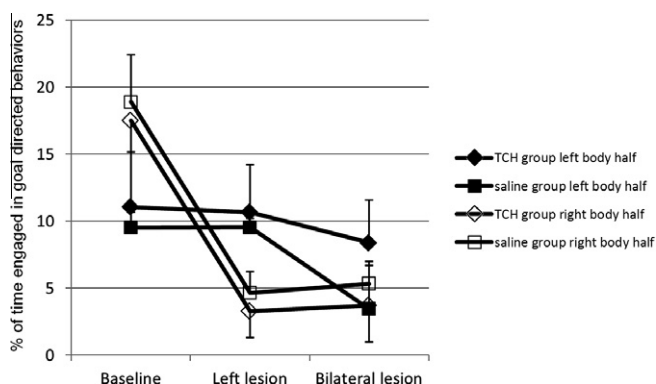


Fig. 1. Goal directed limb movements (% of the time) in the four treatment groups over time.

detected and mean parkinsonian symptoms scores were 0. Monkeys spent more time on right than on left limb movements (Fig. 1 and Table 2).

Administration of MPTP into the left carotid artery induced right-sided parkinsonism in all monkeys (Fig. 1 and Table 2) as described previously (Andringa et al., 2003), resulting in an increase of mean parkinsonian symptoms scores. The amount of limb movements on the right body half decreased, while the amount of left sided limb movements remained in the same range as in the baseline stage (Fig. 1 and Table 2).

In the saline treated group the second infusion of MPTP into the right carotid artery induced parkinsonism on the left side of the body, thus increasing the mean parkinsonian symptoms scores (Table 2). In the four monkeys receiving TCH346, no parkinsonism developed on the left side of the body, and mean parkinsonian symptoms scores remained unchanged. These effects have been described in detail elsewhere (Andringa G., 2000; Andringa et al., 2003). The severity of parkinsonian signs on the right body side was unaffected by the second MPTP treatment. Time spent on left limb movements was reduced in the saline group, but not in the TCH346 treated group. Also, no effect was noticed of the second infusion of MPTP on right limb movements.

3.3. Correlation between motor symptoms and [^{18}F]-F-DOPA uptake

Mean parkinsonian symptoms scores were highly significantly and negatively correlated with mean striatal uptake of

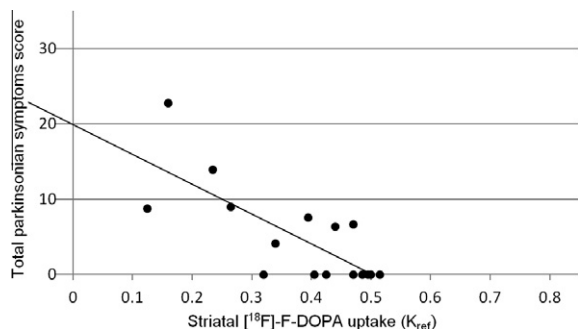


Fig. 3. Highly significant negative correlation between mean striatal [^{18}F]-F-DOPA uptake (K_{ref}) and total parkinsonian symptoms scores. (Spearman's $\rho = -0.735$, $p = 0.001$). Both observations from eight monkeys were treated as independent.

Table 3

Correlations (ρ -Spearman's rho) between striatal [^{18}F]-F-DOPA uptake (K_{ref}) and behavioral data. Correlations were calculated over Baseline and Bilateral lesion stages.

Correlation	ρ	p
Mean striatal [^{18}F]-F-DOPA Uptake vs. total parkinsonian symptoms scores	-0.735	0.001
Left striatal [^{18}F]-F-DOPA Uptake vs. right limb movements	0.576	0.019
Right striatal [^{18}F]-F-DOPA Uptake vs. left limb movements	0.333	0.208

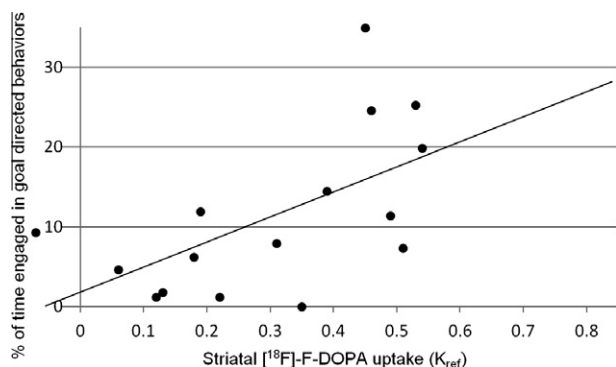


Fig. 4. Significant positive correlation between left striatal [^{18}F]-F-DOPA uptake (K_{ref}) and right limb movements (% of the time). (Spearman's $\rho = 0.576$, $p = 0.019$). Both observations from eight monkeys were treated as independent.

[^{18}F]-F-DOPA as indicated by Spearman's rho (see Fig. 3 and Table 3).

A significant positive relationship was found between left striatal [^{18}F]-F-DOPA uptake and right limb movements (Fig. 4 and Table 3).

The relationship between right striatal [^{18}F]-F-DOPA uptake and left limb movements was not significant (Table 3).

Linear fits were not statistically significantly different from non-linear fits.

4. Discussion

4.1. Validity of [^{18}F]-F-DOPA scanning in MPTP monkeys

Not many studies have systematically correlated motor symptoms with striatal [^{18}F]-F-DOPA uptake in the MPTP lesioned monkey in a longitudinal design. This is relevant because the MPTP

monkey is a highly valid PD model and [^{18}F]-F-DOPA is used in the clinic to monitor the degradation of nigrostriatal system function within individual PD patients.

We found significant correlations between: (i) total parkinsonian symptoms scores and mean striatal [^{18}F]-F-DOPA uptake and between (ii) lateralized limb movements and contralateral [^{18}F]-F-DOPA uptake in MPTP lesioned monkeys (for left striatum and right limbs).

This finding of significant correlations between motor scores and dopamine function in MPTP-lesioned monkeys is in agreement with previous studies using [^{123}I]- β -CIT SPECT (Eberling et al., 1999) and [^{18}F]-FMT PET (Eberling et al., 1998; Eberling et al., 2000). Our data are also in agreement with a previous study (de Yebenes et al., 1998) which showed that in MPTP lesioned monkeys there was a correspondence between motor behavior and [^{18}F]-F-DOPA uptake. We extended this study to a three-scan design and by adding a statistical analysis of the correlation between motility and [^{18}F]-F-DOPA uptake. Similarly, we extended the previous finding that significant correlations exist between striatal [^{18}F]-F-DOPA uptake and motor behavior across monkeys (Blesa et al., 2010) to the within subjects situation where the same monkeys are scanned repeatedly.

We confirm that behavioral observation by means of video-taping and a qualitative rating scale is a sensitive and reliable tool for assessment of nigrostriatal function in monkeys (Saiki et al., 2010) and also that it correlates with neurochemical properties of the dopaminergic system as measured with PET (Saiki et al., 2010).

A recent study in PD patients (de la Fuente-Fernández, 2012) reported that the accuracy of a clinical diagnosis of PD is very high and identical to the accuracy of a SPECT based diagnosis. This is in agreement with the findings presented here because our behavioral and neurochemical endpoints were also both very accurate at identifying animals with dopaminergic lesions.

4.2. Methodological considerations

The two different treatment regimes in terms of TCH346 resulted in a wide range of severity of the MPTP lesions and therefore also in striatal [^{18}F]-F-DOPA uptake and parkinsonian motor signs. Such a wide range in motor dysfunction and [^{18}F]-F-DOPA uptake is advantageous for a regression analysis on these parameters.

We assumed that TCH346 does not alter the relationship between striatal dopaminergic uptake and motor behavior, as both are altered in a consistent manner. This is supported by the finding that the correlations between motor scores and striatal uptake were similar in all treatment groups. However, this has not been tested with experimental data and a possible effect of TCH346 on the relation between the two parameters cannot be ruled out.

In the non-lesioned phase we found a mean K_{ref} of 0.002. This is in the same range as the results of others (Doudet et al., 1999). The fact that some of our K_{ref} values were negative is due to the fact that K_{ref} is a random variable with random noise so that the 'spot estimate' can be negative if the true K_{ref} is zero or close to zero.

The correlation between right sided striatal [^{18}F]-F-DOPA uptake and left limb movements was not statistically significant. The lack of significance is explained by the fact that all monkeys were right-handed so that the values for left limb movements were half as large as the contralateral movement values. Also, the left MPTP dose was half as large as the right dose.

In our statistical analyses, we considered all data points as independent observations, although these are not completely independent from each other because they are obtained from the same animals. However, the intra-individual dependence largely disappears with each administration of MPTP.

4.3. Summary

In conclusion, striatal [^{18}F]-F-DOPA uptake correlates with behavioral measures in MPTP-treated monkeys, not only in parallel but also in longitudinal experimental designs. Both [^{18}F]-F-DOPA PET and quantitative objective behavioral assessment are robust and reliable methods for assessing the functional integrity of the nigrostriatal dopaminergic system.

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